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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/877,832 | 06/07/2001 | Jean-Damien Charrier | VPI/00-117 | 9982 |

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| EXAMINER |
|---|
| BALASUBRAMANIAN, VENKATARAMAN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 10/21/2002

7

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/877,832 | CHARRIER ET AL. | |
| | Examiner | Art Unit | |
| | Venkataraman Balasubramanian | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's election with traverse of invention of Group I, claims 1-13 in Paper No. 6, is acknowledged. Claims 1-13 will be examined to the extent they embrace the elected subject matter.

Applicants' traversal of restriction requirement is fully considered but deemed as not persuasive for reasons of record. As for the traversal, the following apply.

1. Contrary to applicants' urging, both the criteria of distinct and independent invention and search burden are clearly presented in the previous office action. To summarize, principles of classification dictate that ring structures having different numbers of heteroatoms to be classified in different classes. Such classification, as noted in the previous office action, stems from the fact that the ring structures have different properties, different reactivities and different effects on the substituents. They are made and used differently. Hence each invention is distinct and independent. Furthermore, applicants have not asserted that the core groups are all equivalent. In which case, prior art which anticipates instant elected invention may then render the non-elected inventions as obvious variant and can thus be applied.

2. Again contrary to applicants' urging, searching all core groups with varying ring size and different hetero atoms as required for A and C ring along with the variation of B ring would be serious search burden given the fact that only limited time is available for examination of each application.

The requirement is still deemed proper and is therefore made FINAL

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of the term "derivative" in claim 1 renders the claim indefinite, as the structural make-up of the derivative is not known. Note the term "derivative" can include any organic group bearing the instant core what is intended. Note term "derivative" implies more than what is being positively recited therein.
2. Recitation of the term " isosteres thereof" in claim 1, renders the claim indefinite, as the term "isosteres" is vague and unclear. It is not clear what is really intended. Is it the isosteres of carboxylic acid group or the isosteres of the rest of the choices recited therein? Is the isosteres include other choices then an enablement issue will arise as specification limits the isosteres to that of carboxylic acid group and there is no suggestion as to what isosteres of amide or esters are intended.
3. Recitation of the term "features" in claim 2 is vague as the term creates ambiguity. Its replacement with group is suggested.
4. Claim 5 is objected to as refers to a Table in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preserving cells or organs or treating arthritis with the instant compound, does not reasonably provide enablement for various diseases embraced in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant compounds are disclosed to have caspase activity and it is recited that the instant compounds are useful, besides in preserving cells and organs, are useful for all or any diseases including those yet to be discovered as due to caspase for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibition of interleukin-12 overproduction of provided in the specification at pages 14-18. The instant compounds are disclosed to have inhibiting activity on interleukin-12 overproduction and it is recited that the instant compounds, at the time of the instant invention, are therefore useful in treating any or all diseases where interleukin-12 is implicated, for which applicants provide no competent evidence. From the reading of specification, it appears that the applicants are asserting that the embraced compounds because of their mode action which involves inhibition of caspase activity would be useful for all sorts of diseases including inflammatory diseases autoimmune diseases, bone diseases, proliferative diseases, degenerative diseases sepsis, psoriasis,

rheumatoid arthritis, multiple sclerosis etc. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host- warm blooded animal. The fact that a single class of compounds can treat all diseases is incredible and applicants have not provided any supporting evidence or enabling disclosure. Moreover many if not most of diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease HIV etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or

lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating a condition or disease related caspase activity.

2) The state of the prior art: The publications cited in the Information Disclosure Statement expressed, at the time of the instant invention was made, that treating disease by the inhibition of caspase is still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibiting caspase are unpredictable and at best limited to modulation of arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related caspase activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bemis et al. WO 95/35308.

Bemis et al. teaches several inhibitors of interleukin-1β converting enzyme, which include compounds claimed in the instant claims for the treatment of various diseases. See formula α on page 26 and note the definition of various variable groups, especially note $R_1$ can be a tricyclic pyrimidinone as required by the instant claims. See pages 138-166 for various pyrimidinone compounds.

Instant claims require variously substituted tricyclic pyrimidinone.

Bemis et al. teaches the equivalency of exemplified compounds with those claimed tricyclic pyrimidinone with various substituents in the definitions of various varible groups. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in tricyclic pyrimidinone ring and the and the side chain as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

References cited in the Information Disclosure Statement (paper #5) are made of record.

***Conclusion***

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

10/19/2002